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14. ABSTRACT
The ability to accurately and efficiently monitor the neurocognitive status of US warfighters under diverse operational and experimental conditions is of critical importance to the ongoing mission and network-centered initiatives of the United States military. The Automated Neuropsychological Assessment Metrics (ANAM) is a computer assisted tool for evaluating neurocognitive performance with demonstrated effectiveness for application in diverse military operational and research testing scenarios. The primary objective of this project is to examine select psychometric and administration properties of the newly-released ANAM4. Four studies are proposed that will 1) examine common use practices and determine the effect of specific administration procedures on ANAM4 performance, 2) assess the test-retest reliability of individual ANAM4 tests, 3) examine the validity of the ANAM4 mood scale, and 4) develop a representative normative dataset for Army National Guard service members. Data collection is complete for Studies 1, 2 and 3; data analysis and manuscript preparation is underway for all three studies. Data collection is underway for Study 4.

15. SUBJECT TERMS- ANAM, neurobehavioral, assessment, psychometrics, validity, reliability, normative

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INTRODUCTION

The ability to accurately and efficiently monitor neurocognitive status of U.S. warfighters under diverse operational and experimental conditions is of critical importance to the ongoing mission and network-centered initiatives of the U.S. military. The Automated Neuropsychological Assessment Metrics Version 4 (ANAM4) is a computer-assisted tool for evaluating neurocognitive performance with demonstrated efficacy for application in diverse military operational and research testing scenarios. The primary objective of this multi-study project is to examine select psychometric and administration properties of the ANAM4. This project includes four studies that will i) examine common use practices and determine the effect of specific administration procedures on ANAM4 performance (Study 1), ii) assess the test-retest reliability of individual ANAM4 tests (Study 2), iii) examine the validity of the ANAM4 mood scale (Study 3), and iv) develop a representative normative dataset for Army National Guard Service members (Study 4).

Body

This project was funded 01 December 2007. The approved study timeline/SOW is presented in **Table 1.**

A request for a 12 month no-cost extension for this study was approved on 7 November 2012, extending study activities through December 2013. A modified statement of work, approved as part of the no-cost extension and currently pending approval by the USARIEM HURC (Amendment #14), is presented in **Table 2**.

Table 1: Statement of Work/Study Timeline

Year 1	**Months 1-2**	**Task 1**	Plan and finalize logistics for Phase I (Studies 1-3)
	Months 3-12 (Dec 2008)	**Task 2**	Subject recruitment, data collection and data management for Studies 1-3
Year 2	**Month 13-14**	**Task 3**	Perform preliminary data analyses for Study 3
	Month 15-24 (Dec 2009)	**Task 4**	Complete data collection for Study 1
		Task 5	Perform preliminary data analyses for Study 1
		Task 6	Continue recruitment, data collection and data management for Study 2 & 3
		Task 7	Complete data collection for Study 3
Year 3	**Month 25-36 (Dec 2010)**	**Task 8**	Complete data collection for Study 2
		Task 9	Plan and finalize logistics for Phase II (modified Study 4)
		Task 10	Complete data analyses for Studies 1, 2, 3
		Task 11	Preparation of journal manuscript(s) for Studies 1, 2, 3
		Task 12	Preparation of Project report for Studies 1, 2, 3
		Task 13	Set-up data management procedures for Study 4
Year 4	**Month 37-48 (Dec 2011)**	**Task 14**	Initiate data collection procedures for Study 4
		Task 15	Carry out data collection procedures for Study 4
		Task 16	Initiate integrative data management structure set up for Study 4
		Task 17	Operationalize database for Study 4 analysis scheme
		Task 18	Perform preliminary data analyses for Study 4
		Task 19	Complete data collection procedures for Study 4
Year 5	**Month 49-60 (Dec 2012)**	**Task 20**	Complete data analyses for Study 4
		Task 21	Prepare Study 4 manuscript(s) for peer review
		Task 22	Preparation of Project Final Report

Table 2: MODIFIED SOW for remaining PROJECT Tasks and STUDY TIMETABLE

Year 4	**Month 37-48 (ending Dec 2011)**	**Task 14**	Initiate data collection procedures for Study 4
		Task 15	Carry out data collection procedures for Study 4
		Task 16	Initiate integrative data management structure set up for Study 4
		Task 17	Operationalize database for Study 4 analysis scheme
Year 5	**Month 49-60 (ending Dec 2012)**	**Task 18**	Conduct data collection procedures for Study 4 (cont'd)
		Task 19	Complete manuscript preparations/submissions for Studies 1-3
		Task 20	Set up/operationalize data analyses plan for Study 4
Year 6	**Month 61-72 (ending Dec 2013)**	**Task 21**	Complete data collection for Study 4
		Task 22	Complete data analyses for Study 4
		Task 23	Prepare Study 4 manuscript(s) for peer review
		Task 24	Preparation of Project Final Report

Task 1 (Month 1-2)
Plan and finalize logistics for Phase I (Studies 1-3) – COMPLETED
All logistical aspects for HURC approved studies (Studies 1-3) have been confirmed. Recruitment procedures, equipment, testing facilities, and other data collection elements have been finalized and are now complete

Task 2 (Month 3-12) Subject recruitment logistics, data collection and data management for Studies 1-3 – Completed
Subject recruitment, data collection and data management efforts have been completed for Studies 1-3. Recruitment of both Human Research Volunteers and Civilians was effective and efficient.

Task 3 (Month 15-24) Perform preliminary data analyses for Study 3– COMPLETED
All preliminary data analyses for Study 3 have been completed. Initial analyses suggested that additional participants would be necessary to explore noted differences between military and civilian participants on discrete on mood measures. Thus an amendment (#4, 14 July 2009) to increase enrollment from 50 to 80 participants was submitted and approved. Higher-level analyses are nearing completion on this expanded sample.

Task 4 (Month 15-24) Complete data collection for Study 1– COMPLETED
Study 1 involves the examination of common use practices and specific administration procedures (individual or group administration, practice or no practice, single session or two sessions) on ANAM4 task performances. Our recruitment goal for Study 1 was 90 participants, 30 participants per condition. This goal has been reached. Enrollment data are presented in **Table 3**.

Table 3. Study 1 Enrollment

# Participants Enrolled	90
# Participants Completed	86*

**NOTE: 15 participants completed the ANAM4 without practice test modules; 15 participants completed the ANAM4 in a group setting and 15 participants completed the ANAM4 in two administration sessions. The remaining 41 participants served as controls for these discrete administration scenarios (individual administration using practice test modules and completed in a single testing session). Thus each condition had at least 30 participants, as required.*

Task 5 (Month 15-24) Perform preliminary data analyses for Study 1 – COMPLETED
Preliminary analyses (sample characterization and demographic analyses) on the Study 1 data set have been completed.

Task 6 (Months 15-24) Subject recruitment, data collection and data management for Studies 2 & 3 – COMPLETED
Our recruitment goal for Study 2 was 90 participants, 30 participants per condition (days 1 & 7 / days 1 & 30 / 7 consecutive day retest). Recruitment goal for Study 3 was 80 participants. Recruitment goals were reached for Studies 2 and 3 and data collection has been completed for these studies.

Task 7 (Months 15-24) Complete data collection for Study 3 – COMPLETED
Data collection for Study 3 is complete. Enrollment data are presented in **Table 4**.

Table 4. Study 3 Enrollment

# Participants Enrolled	113
# Participants Completed	77

Task 8 (Months 25-36) Complete data collection for Study 2- COMPLETED
Data collection for Study 2 is complete. Enrollment data are presented in **Table 5**.

Table 5. Study 2 Enrollment

# Participants Enrolled	99
# Participants Completed	92

Task 9 (Months 25-36) Plan and finalize logistics for Phase II (modified Study 4) – COMPLETE
The Study 4 protocol has been reviewed and approved by USARIEM HURC and HRPO (final approval to initiate received June 2011). Endorsement of the study by the National Guard Bureau (NGB) was received 20 October 2011 and all 8 states (Arizona, Kentucky, Maine, Minnesota, Mississippi, Montana, Oklahoma, Pennsylvania) have been contacted by both NGB and study staff. Oklahoma declined participation in September 2012. We identified Texas as a suitable replacement for Oklahoma and secured NGB endorsement for the state in October 2012. We are currently working with the Texas ARNG State Surgeon's office to secure approval for the study.

The study protocol is currently being reviewed by the ARNG Adjutant General from the state of Minnesota.

Task 10 (Months 25-36) Complete data analyses for Studies 1, 2, 3 - IN PROGRESS
Preliminary data analyses have been completed for each of the studies. We are currently conducting higher-level analyses for data within each of these studies.

Task 11 (Months 25-36) Preparation of journal manuscript(s) for Studies 1, 2, 3 – IN PROGRESS
Manuscripts for each of these studies are in draft form and are waiting for completion of higher-level analyses to finalize and submit to peer-reviewed journals.

Task 12 (Months 25-36) Preparation of project report for Studies 1, 2, 3 – COMPLETED
Project summaries and completion of Studies 1-3 were included in previous continuing review reports. Manuscripts for these studies are in progress.

Task 13 (Months 25-36) Set-up data management procedures for Study 4 - COMPLETED
All procedures involving data management have been established. Study datasets have been created and are being populated as data are obtained from field sites. Data entry and checking have been successfully coordinated.

Task 14 (25-36) Initiate data collection procedures for Study 4 – IN PROGRESS
Data collection procedures were initiated in Arizona in the prior reporting period. Planning activities for data collection trips to Montana and Maine were initiated during this reporting period, with an initial data collection trip completed in November of 2012.

Task 15 (37-48) Carry out data collection procedures for Study 4 – IN PROGRESS
Data collection in AZ continued during this reporting period, with one data collection trip (2 sites) completed. Data collection in Maine was initiated in November of 2012 and one trip was completed during this reporting period.

Current enrollment by state is presented in **Table 6**.

Table 6: Current Study 4 enrollment

State	# Completed
Arizona	146
Maine	45
Total	**191**

Task 16 (37-48) Initiate integrative data management structure set up for Study 4 - COMPLETED
Databases associated with Study 4 data have been created and are being populated as data are obtained.

Task 17 (37-48) Operationalize database for Study 4 analysis scheme – IN PROGRESS

Data entry has commenced and databases continue to be refined for analytic schemes.

Task 18 (37-48) Perform preliminary data analyses for Study 4 - PENDING

Task 19 (49-60) Complete data collection procedures for Study 4 - PENDING

Task 20 (49-60) Complete data analyses for Study 4 – PENDING

Task 21 (49-60) Prepare Study 4 manuscript(s) for peer review – PENDING

Task 22 (49-60) Preparation of Project Final Report – PENDING

KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments during the current study period include:

- Preliminary data analyses for Studies 1-3 are complete. Higher-order analyses are underway for Studies 1 & 2. Manuscript preparation is underway for Studies 1-3, with Study 3 manuscript near completion.

- Continuing Review report was reviewed and approved by the USARIEM HURC (8 March 2012).

- To date, three out of eight states have agreed to participate in Study 4 data collection and provided TAG-level approval; approvals are pending (expected) in two additional states.

    - Data collection continued in two states during this reporting period: Arizona (1 trip completed) and Maine (1 trip completed). An additional trip to Maine (February 2013) and data collection trips to Montana in December 2012 (completed), January and February 2013 have been coordinated/scheduled; these and other future trips will be documented in the Final Report (Dec 2013).

REPORTABLE OUTCOMES

Reportable outcomes during the current reporting period include:

1. Reports, manuscripts, abstracts (Appendix)
The following manuscripts, published during this reporting period, were supported in part by this award (W81XWH-08-1-0021):

- Scherer MR, Claro PJ, Heaton KJ. Sleep Deprivation Has No Effect on Dynamic Visual Acuity in Military Service Members Who Are Healthy. Phys Ther. 2012 Nov 15;. [Epub ahead of print] PMID: 23162043.
- Maruta J, Heaton KJ, Kryskow E, Maule A, Ghajar J. Published online 07 Sep 2012. Dynamic Visuo-motor Synchronization: Quantification of Predictive Timing. *Behavior Research Methods.* DOI 10.3758/s13428-012-0248-3

2. Degrees and research training opportunities
Two PhD-candidates, two individuals with Masters degrees, and five individuals with bachelor degrees have been trained to administer the study protocol for this project.

3. Collaborative funding applications related to work supported by this award
The following funded projects are directly related to the work supported by this award:

- ✓ "Eye-Tracking Rapid Attention Computation (EYE-TRAC)" (USARIEM Protocol # H09-07). This project was funded as a FY08 CDMRP Advanced Technology Award to Dr. Jamshid Ghajar, Brain Trauma Foundation, New York, NY (W81XWH-08-2-0646). Dr. Kristin Heaton is the USARIEM site Principal Investigator. This project includes an ANAM4 task battery (ANAM 4 TBI Battery) as part of the protocol, with ANAM 4 data being collected at 4 time points, allowing for computation of test-retest reliability across a 2 week interval and sensitivity of the ANAM4 TBI battery to differentiate performance between a rested and fatigued (24 hour sleep deprivation) state. This project is ongoing.

- ✓ "An Investigation of the Effects of Head Impacts Sustained during Collegiate Boxing Participation on Central and Peripheral Nervous System Function" (USAFA Protocol # FAC2007010H, PI: MAJ Brandon Doan, USAFA), was funded in part by an AMEDD Advanced Medical Technology Initiative (AAMTI) award to Dr. Heaton and includes use of the ANAM4. Data collection is complete; manuscripts are in progress.

- ✓ "Validation of Select Neurobehavioral Assessments for Concussion/Mild Traumatic Brain Injury (MTBI)" (USARIEM #H09-08), was intramurally funded (MRMC RAD3) to Drs. Proctor and Heaton (co-PIs). This study seeks to validate the ANAM4TBI Battery against a standard neuropsychological screening battery for mild traumatic brain injury. The project is ongoing.

- ✓ "Identifying biomarkers that distinguish post-traumatic stress disorder and mild traumatic brain injury using advanced magnetic resonance spectroscopy," was funded via a Department of Defense Congressionally Directed Medical Research Programs

Psychological Health/Traumatic Brain Injury (PH/TBI) Research Program award to Dr. Alex Lin, Brigham and Women's Hospital, Boston, MA. Dr. Heaton is a co-Investigator and site PI on this project. This study proposes a multi-parametric approach using major advances on spectroscopic methods and neuroimaging to identify biomarkers that can be used to distinguish between post-traumatic stress disorder, traumatic brain injury, and their co-occurrence. This will be achieved in part by correlating quantitative MR spectroscopy results with behavioral and neuropsychological metrics (including ANAM4) using newly developed algorithmic approaches that are capable of revealing discriminating metabolic markers in MR spectroscopy measurements. The funding period for this project is 11/10-10/13; the protocol is currently under IRB review.

4. Related projects and collaborations initiated

- ✓ "Analyses of ANAM4 TBI predeployment assessment data: USARIEM-OTSG research collaborative" (USARIEM Protocol 11-07-HC) (PI: Dr. Proctor; Co-I: Dr. Heaton)
- ✓ "Identifying biomarkers that distinguish post-traumatic stress disorder and mild traumatic brain injury using advanced magnetic resonance spectroscopy," (2007-P-002458/9; Brigham and Women's Hospital) Department of Defense U.S. Army Medical Research and Material Command Congressionally Directed Medical Research Programs, 2009 Psychological Health and Traumatic Brain Injury Research Program Award (PI: Dr. Alexander Lin, Brigham and Women's Hospital; Co-I: Dr. Heaton)

- ✓ "Noninvasive Cerebral Glutamate Monitoring in Veterans with Traumatic Brain Injury" Harvard Catalyst Pilot Grant, (PI: Dr. Alexander Lin, Brigham and Women's Hospital; Co-I: Dr. Heaton)

- ✓ Massachusetts Institute of Technology Lincoln Laboratories: collaborations with Dr. Heaton aimed at developing multi-modal assessments for mild TBI/concussion (with Jonathan Su, Ph.D., Laurel Reilly-Raska, Ph.D.), and validation of novel biophysiologic measures of fatigue, brain injury, and stress (with Tom Quatieri, Ph.D., Nick Malyska, Ph.D.).

CONCLUSIONS

There has been steady and significant progress in this current funding period. Data from Studies 1-3 are being analyzed and manuscripts are being prepared for submission to peer-reviewed journals. Study 4 has been approved by both USARIEM HURC and HRPO. National Guard Bureau has provided endorsement of the study and all eight identified states have been contacted. Data collection has continued in AZ and commenced in ME, and was coordinated for December-February in Montana. One state declined participation (OK) and was replaced by Texas, following endorsement of the change by the National Guard Bureau; an amendment to the USARIEM protocol is currently under review. TAG approval is also pending for the state of MN.

Data from this project will contribute to ongoing efforts to validate the ANAM4 and inform use of this assessment tool and interpretation of testing results within a military population.

APPENDIX

Sleep Deprivation Has No Effect on Dynamic Visual Acuity in Military Service Members Who Are Healthy

Matthew R. Scherer, Pedro J. Claro and Kristin J. Heaton

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Military Rehabilitation Special Series

Sleep Deprivation Has No Effect on Dynamic Visual Acuity in Military Service Members Who Are Healthy

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Background. The risk of sustaining Traumatic Brain Injury (TBI) and co-morbid post traumatic dizziness is elevated in military operational environments. Sleep deprivation is known to affect Service Member performance while deployed though little is known about its effects on vestibular function. Recent findings suggest that moderate acceleration step rotational stimuli may elicit a heightened angular vestibulo-ocular reflex (aVOR) response relative to low frequency sinusoidal stimuli after 26 hours of sleep deprivation. There is concern that a sleep deprivation-mediated elevation in aVOR function could confound detection of co-morbid vestibular pathology in Service Members with TBI. Dynamic Visual Acuity (DVA) refers to one's ability to see clearly during head movement and is a behavioral measure of aVOR function. The Dynamic Visual Acuity Test (DVAT) assesses gaze instability by measuring the difference between head-stationary and head-moving visual acuity.

Objective. The purpose of this study was to investigate the effects of 26 hours of sleep deprivation on DVA as a surrogate for aVOR function.

Methods. 20 Soldiers with no history of vestibular insult or head trauma were assessed using the DVAT at angular head velocities of 120-180 degrees/ second. Active and passive yaw and pitch impulses were obtained before and after sleep deprivation.

Results. Yaw DVA remained unchanged due to sleep deprivation. Active pitch DVA diminished by -0.005 LogMAR (down) and -0.055 LogMAR (up); and passive pitch DVA was degraded by -0.06 LogMAR (down) and -0.045 LogMAR (up) ($p=0.002$).

Discussion. DVA testing in healthy soldiers revealed no change in gaze stability following rapid yaw impulses and sub-clinical changes in pitch DVA following sleep deprivation. Findings suggest that DVA is not affected by short term sleep deprivation under clinical conditions.

Introduction

The human vestibular system consists of a peripheral sensory apparatus, central processing centers, and efferent pathways which mediate numerous functional motor outputs.[1] Among these, the angular vestibulo-ocular reflex (aVOR) maintains stable gaze (i.e., eye position in space) by generating compensatory eye movement responses which are opposite in direction, but equal in magnitude to head movement stimuli.[2,3] Additionally, cortical vestibular processing centers within the insular and temporoparietal brain regions integrate vestibular, visual and somatosensory signals constructing neural representations of one's environment to accurately guide behavior.[1,3,4]

A growing body of evidence supports an association between vestibular pathology and post-traumatic dizziness in Service Members who sustain mild traumatic brain injury (mTBI) in the deployed environment.[2,5-7] According to official Department of Defense sources, over 220,000 Service Members have been diagnosed with TBI within the last decade leading some to describe this condition as the "signature injury" of modern conflicts.[8-10] Epidemiological findings for a returning Brigade Combat Team indicated that 22.8% of Soldiers in the unit had at least one clinician-confirmed TBI over the course of a year-long deployment. Among symptoms experienced in this sub-group of injured personnel, post-traumatic dizziness (59.3%) and balance problems (25.9%) were exceeded in prevalence only by headache.[11] Similar findings have been documented elsewhere in the literature.[12-14]

Like other sensorimotor sequelae associated with mTBI, vestibular dysfunction can be challenging to assess in the deployed environment where sophisticated measurement techniques are typically not available. Accurate assessment may be further complicated by situational or environmental stressors which are known to affect performance in military operational settings.[15]

Sleep disturbances in deployed environments have been shown to contribute to battle fatigue, degraded operational performance, and potentially insidious (and dangerous) lapses in vigilance or "situational awareness" in military parlance.[15-18] While the effects of sleep deprivation on executive function, memory, and reaction time are well established, little is known about the effects of sleep deprivation on vestibular function, a sensory modality also critical for perceptual stability in military operational environments.[4,19-21]

Few studies have investigated the effects of sleep deprivation on aVOR function and early work did not identify significant changes in eye movement responses to rotational stimuli following short-term (24-28 hours) sleep deprivation protocols.[22,23] There is however, one notable exception to this trend. Quarck and colleagues explored the effects of 26 hours of supervised sleep deprivation on aVOR function using two distinct rotational chair testing paradigms.[24] In one of these, subjects were rotated with a velocity step from 0 to 60 degrees/ second (angular acceleration 100 degrees/ second^2) in clockwise and counter clockwise directions. Eye movements were recorded using electo-nystagmography. In a second, independently administered condition, participants were sinusoidally rotated at a velocity of ±25 degrees/ second and a frequency of 0.2 Hz (maximum chair acceleration was 0.32 degrees/ second^2). Findings from these experiments revealed a significant post- sleep deprivation elevation in aVOR gain (eye/ chair velocity) relative to a baseline (well-rested) condition for *step rotations* but not sinusoidal testing. The authors of this study proposed that the abrupt onset of rotation during step testing in conjunction with sleep deprivation- induced modulation of the temporoparietal junction resulted in the enhanced vestibular response.[24] This theory is plausible because the temporoparietal junction is an area of known importance both for regulating the

VOR and for detecting unexpected, potentially destabilizing, or novel stimuli.[24-26] To our knowledge, the effects of sleep deprivation on behavioral measures of gaze stability have not been investigated elsewhere. If it holds true however, that sleep deprivation consistently *elevates* aVOR responses to moderate and high-acceleration rotational stimuli, such a finding could represent a significant diagnostic impediment to accurate vestibular assessment in deployed clinical environments where sleep disturbances are commonplace.[18] As such, there is a pressing need to identify the effects of sleep deprivation on gaze stability in Service Members.

The most commonly used clinical measure of gaze stability is dynamic visual acuity (DVA) which refers to one's ability to see clearly during head movement.[27] The dynamic visual acuity test (DVAT) is a behavioral measure of aVOR function used to characterize gaze instability under functional (i.e., high velocity and acceleration) conditions by measuring the difference between head stationary and head moving visual acuity.[27] While limited research has been performed exploring the psychometrics of this measure, [27,28] [29] the instrumented DVAT is known to be both sensitive (94.5%) and specific (95.2%) for detecting vestibular asymmetry in persons with vestibular dysfunction and has been shown to have excellent test-retest reliability for both yaw (r= 0.87 healthy controls, r = 0.83 patients with dizziness) and pitch (r= 0.89 healthy controls, r = 0.94 patients with dizziness) plane assessments. [27,28] Reliability testing in healthy study participants is typically conducted over one-week timeframes to reflect common clinical practice patterns for re-assessment. These same studies however, have measured reliability in patient participants within the same day to control for the effects of compensation over time. [27,28] Reliability testing over periods of 24-72 hours (consistent with practice patterns in an operational environment) has not yet been reported in the literature.

Recently, in a study focused specifically on the reliability of commonly used clinical measures of gaze stability, Mohammad and colleagues found improved DVAT test-retest reliability when patients with vestibular disorders were tested twice within one testing session (with 30 minutes of rest between measurements) relative to subsequent assessment 7-10 days later.[29] These findings suggest that the *timing* of DVA re-assessment could impact test reliability if administered at intervals less than one-week from baseline. Timing of DVAT test administration may also be relevant in operational environments where the opportunity for repeat assessment over a one week time frame is not always feasible.[30] Given the necessity for objective outcomes to help guide return-to-duty decision making following TBI/ traumatic dizziness, the known utility of the DVAT for identifying vestibular asymmetry, and the relative dearth of published studies reporting DVAT reliability data for short-term re-assessment, further investigation of test-retest reliability within operationally relevant time parameters is appropriate.

The DVAT is typically administered under active (i.e., participant generated) head movement conditions thought to assess vestibular function in concert with descending efference copy signals from the cortex.[31] Active head impulses are known to speed the latency of the aVOR response although gain values are typically augmented only in the presence of vestibular pathology.[32] The DVAT may also be administered passively with clinician-administered, high acceleration, high velocity, low amplitude head impulses that are unpredictable in timing and direction.[33] Unlike the active or "predictable" DVAT, passive DVA assessment is theorized to isolate peripheral vestibular contributions to gaze stability by eliminating efference copy mediated effects and resultant pre-programmed eye movements.[31] This is accomplished via *examiner mediated* alteration of the predictability, timing, and magnitude of head movement stimuli.[31, 33,34] Recent evidence suggests that complementary measurement of both active and

passive gaze stability may be useful in assessing post-traumatic dizziness given the possible co-occurrence of peripheral and central dysfunction. [2,7] While there is a growing body of evidence supporting the use of passive DVA assessment, reliability of this technique has not yet been reported for yaw or pitch plane assessment. [33,35]

Given strong psychometric properties, clinical feasibility, and demonstrated utility in identifying vestibular asymmetry in vestibulopathic and concussed personnel, the DVAT shows considerable promise for use in forward deployed environments where co-morbid mTBI, post traumatic dizziness, and sleep deprivation are prevalent.[13,27,36,37] The primary purpose of this study was to investigate the effect of 26 hours of supervised sleep deprivation on DVA in uninjured Active Duty Service Members. Additionally, we explored the test-retest reliability of the DVAT for assessing aVOR function during an operationally relevant, 24 hour period during which time participants were rested. We hypothesized that DVA would not be significantly affected by 26 hours of supervised sleep deprivation.

Method

Participants

We studied 20 US Army Soldiers (18 males, 2 females; mean age 21.7 $\pm$ 3.3 years, range 18-28 years) with no history of TBI or vestibular pathology in a US based laboratory environment. Selection criteria for participants excluded those with prior history of substance abuse, known neurological disorders, and known psychiatric conditions (including attention deficit disorder, post-traumatic stress disorder). Participation required no gross visual (no worse

than 20/30 corrected or uncorrected) or hearing problems and was limited to men and women 18 to 50 years of age, who had completed at least 12 years of education.

Participants all demonstrated full, pain-free active cervical range of motion (including rotation, flexion, and extension) and underwent prophylactic vertebral artery testing. High acceleration, high velocity, low amplitude head impulse testing was also performed on all volunteers to rule out vestibular hypofunction.[34] Screening revealed no abnormalities in this study sample. Informed consent was obtained from all participants in accordance with policies and procedures established by the Institutional Review Board of the US Army Research Institute of Environmental Medicine who approved the study.

Dynamic Visual Acuity (DVA) Testing

After a standardized task familiarization period consisting of 4-5 non-experimental trials per subject to ensure consistent activation of the rate-triggered optotype, participant DVA was randomly assessed in response to both active (alternating/ self-generated) and passive (unpredictable timing and direction/ examiner-administered) head movement stimuli using a commercially available system (Micromedical Technologies, Chatham, IL). DVA testing involved discretely performed (i.e., non-continuous) yaw (left and right) and pitch (up and down) plane head impulses administered in four distinct conditions (i.e., active yaw, passive yaw, active pitch, and passive pitch). In each test condition, participants were instructed to actively return to, or passively submit to a return to a "neutral" *start position* (characterized by zero degrees of cervical rotation) before initiation of the next impulse. Impulse parameters were low in amplitude (~20 degrees) and high in velocity (120-180 degree/second). 120 degrees/ second was chosen as the minimum threshold for optotype presentation to ensure that gaze stability was

driven by the aVOR.[27] Passive impulses were administered by a physical therapist with 8 years of experience with this technique. For testing, participants were seated 10 feet in front of a 20" color monitor which was adjusted to ensure that the visual stimulus was triggered at eye-level. Individuals requiring corrective lenses for normal viewing were instructed to wear them during all testing sessions.

Static visual acuity was measured first by repeatedly displaying a single optotype (the letter C), randomly re-oriented with each trial to 0, 90, 180 or 270 degrees on a computer monitor. Subjects viewed five optotypes starting at the smallest possible font size (corresponding with the greatest possible visual acuity level, 20/10). Static visual acuity was established when a participant could correctly identify all five optotype presentations at a given visual acuity level. Each level of visual acuity was measured in 0.1 LogMAR units (logarithm of the minimum angle of resolution, log10 X, where X = the minimum angle resolved, in arcmin, with 1 arcmin = 1/60 degrees) [25]. The better one's visual acuity, the lower one's LogMAR score, with approximate (rounded) LogMAR scores of -0.3, -0.1, 0, 0.2, 0.3, 0.7, 1.0 corresponding to Snellen visual acuity of 20/10, 20/15, 20/20, 20/30, 20/40, 20/100, 20/200. Negative LogMAR scores denote visual acuities better than 20/20 (i.e., less than 0.00 LogMAR). The ability to assess participant visual acuity at levels better than 20/20 (in both head-static and head-moving conditions) using the Micromedical DVAT reflects a system capability not available in earlier DVA testing studies. [27,28]

For the dynamic component of the test, a single-axis rate sensor was positioned on the subject's head so that the sensor's axis of maximum sensitivity was aligned with the axis of rotation for yaw and pitch plane head movements - axial and interaural axes respectively. During each head rotation, an optotype 'C' pseudo-randomly oriented in one of four directions on the

monitor when head velocity, sensed by the rate sensor, exceeded 120 degrees/second. For each testing condition (i.e., yaw-left, yaw-right, pitch-up, and pitch-down) the optotype would only present (i.e., be visible) for head movements in the designated direction and for the duration of the head movement. For example, the optotype in the pitch-up condition only flashed when cervical extension velocity exceeded 120 degrees/ second during an upward impulse. Within each testing condition there were also head impulses directed toward the non-optotype flashing side to decrease predictability during passive impulse conditions.

The size of an optotype was determined by the participant's success at correctly identifying the orientation of all previously displayed optotypes. All participants were initially assessed at their previously established static visual acuity rating. If unable to correctly identify the orientation of 4/5 optotypes at that level of visual acuity, the size of the optotype was progressively increased by the investigator in 0.1 LogMAR increments (analogous to moving up one line on a Snellen eye chart) until the participant is able to identify 4/5 optotypes at a given level of visual acuity. This event (correct identification of 4/5 optotypes) marked the conclusion of testing for a specific testing condition (e.g., "active yaw left" head movement testing). The DVA test score for each condition (ie., active yaw-left, active yaw-right, passive yaw-left, passive yaw-right, active pitch-up, active pitch-down, passive pitch-up, passive pitch-down) was calculated by subtracting the static visual acuity LogMAR score from the dynamic visual acuity LogMAR score. The difference was expressed in LogMAR and corresponds to the number of lines lost on a standard Snellen Eye Chart. Additional information about LogMAR computation has been published elsewhere.[27] Per accepted clinical standards previously reported in the

literature, a loss of three or more "lines" of visual acuity (9+ optotypes) during dynamic testing would be considered a clinically significant decrement in DVA.[27]

Sleep Deprivation Protocol

Participant DVA was assessed during morning duty hours (i.e., 0800) at three distinct phases within the context of a larger study. During the first testing phase, (T1), well rested participants were instructed on correct performance of the test, given the opportunity to practice active and passive head impulses, and were assessed under all aforementioned head movement conditions. During the second testing phase (T2), well-rested participants were brought back 24 hours after baseline testing to investigate short term stability of the DVAT under similar conditions of alertness as T1 and to assess short-term test-retest reliability. Finally, participant DVA was re-assessed at T3 (T2 + 26 hours) after 26 hours of supervised sleep deprivation.

Participation in the sleep deprivation protocol was limited to four Service Members per testing session. This 26 hour period of sustained wakefulness was performed between T2 and T3 and was conducted under the constant supervision of research personnel to ensure participant safety and compliance. During the 26 hour sleep-deprivation phase, participants were co-located in a common living area and were encouraged to go about their normal daily routine which included exercise, regular meals/ nutrition, and entertainment. Study participants were closely supervised throughout the 26 hour period to ensure compliance with wakefulness guidelines and abstinence from caffeinated products.

Study Design and Data Analysis

This prospective, repeated measures design utilized sleep deprivation as an environmental perturbation to quantify DVA performance within subjects across three levels of

time. SAS 9.2 was used to perform a mixed model analysis with random individual intercept to account for correlation of repeated measurements within participants between conditions. Factors included in the statistical model included independent variables of time (3 levels), head movement condition (2 levels: active vs. passive), and impulse direction (2 levels). Yaw and pitch analyses were performed separately. Planned comparisons were established a priori to investigate the effects of time on DVA performance after 24 hours in a rested condition (measure stability) and again after 26 hours of sleep deprivation Alpha established at 0.05 for each test. While a Bonferroni correction was not prospectively applied to adjust for multiple comparisons, a post hoc correction for the two primary pairwise comparisons (i.e., T1 vs. T2 and T2 vs. T3) would yield a corrected significance level of 0.025. Post-hoc tests were performed to assess for effects of significant 2-way and 3-way interactions between independent variables on the dependent variable (DVA). Time-point comparison calculations for N= 20 subjects, yielded 80% power at the two-sided 0.05 significance level to detect a difference between time-points (i.e., 0.66 times the standard deviation in DVA performance assuming a correlation of 0.5 between time-points, within participants).

Interclass correlation coefficient (ICC 3, 1) was used with 95% Confidence Intervals to assess measure agreement and test-retest reliability over the 24 hour time frame among rested participants (T1 and T2) for each permutation of head movement conditions.

Results

24-Hour Test-Retest Reliability

ICC 3, 1 analysis from T1 to T2 revealed variable levels of agreement between the four head movement conditions. The strength of associations ranged from "poor" to "moderate". [38] Data

for yaw and pitch impulses (to include 95% CI's) are presented in Tables 1 and 2. The Performance data by condition (i.e., active and passive yaw and pitch) for the rested re-assessment are described in greater detail below. Post hoc analysis of between-subjects variance (ANOVA) was not found to be significant (F= 2.02, DF 19, p = 0.171).

Yaw DVA

24-hour reassessment–rested condition. Mean Static visual acuity in the study sample was -0.29 LogMAR (0.30). Absolute Yaw DVA values are presented in Table 3a. While there was a significant time effect (F= 7.08, DF 2, p < 0.001), head movement direction (i.e., left vs. right) (F= 0.41, DF 1, p= 0.52) and head movement type (i.e., active vs. passive, (F= 0.18, DF 1, p = 0.78) did not significantly influence DVA performance for yaw plane impulses (yaw measurements were thus averaged across these head movement direction and movement type conditions). Yaw impulse analysis revealed a statistically significant improvement in DVA (i.e., Yaw DVA) from T1 to T2 (t= 3.60, DF= 216, p = 0.0004) with a mean improvement of -0.04 LogMAR (Log of the minimum angle resolved). This improvement equates to correct identification of 2-3 additional optotypes with the second test (with a change of one optotype equivalent to 0.018 LogMAR of acuity.[28]

Sleep deprived condition. No change in Yaw DVA was identified post sleep deprivation (t=0.90, DF= 216, p = 0.37). Combined yaw plane DVA data and variance for each of the three time points is featured in Figure 1.

Pitch DVA

24-hour reassessment–rested condition. Absolute Pitch DVA values are presented in Table 3b. Pitch analysis revealed overall statistically significant changes in DVA performance for time (F= 7.54, DF= 2, p= 0.0007), head movement type (i.e., active vs. passive, (F= 5.30, DF= 1, p= 0.04) and head movement direction (i.e., "up" vs. "down" , (F= 4.25, DF= 1, p= 0.02) however, tests for 2- and 3- way interaction effects were not statistically significant. DVA differences from T1 to T2 (t= 3.56, p = 0.0005) revealed improvement of 0.025 LogMAR (down) and 0.04 LogMAR (up) under active conditions (the equivalent of two additional optotypes correctly identified in each direction). Passive DVA improved 0.04 LogMAR down (average of 2 optotypes) and 0.015 LogMAR up (~ 1 optotype). Combined pitch plane DVA data for each of the three time points is featured in Figure 2.

Sleep deprived condition. Mean active pitch DVA worsened significantly from T2 to T3 (t= 3.12, p=0.002). Active pitch DVA diminished by -0.005 LogMAR (down) (< 1 optotype) and -0.055 LogMAR (up) (~ 3 optotypes missed). Passive pitch DVA was degraded by -0.06 LogMAR (down) (i.e., ~ 3 optotypes and -0.045 LogMAR (up), an average of 2-3 optotypes missed).

Discussion

Short Term Stability of the DVA Response Under Rested Conditions

Preliminary research supports *weekly* re-assessment of DVA among Service Members in US-based military treatment facilities to guide return-to-duty decisions following TBI .[37] There is presently however, both an operational need for- and a dearth of- objective, evidence based measures to inform such decisions in operational environments. Previous studies report test-retest reliability of the DVAT at time intervals ranging from hours (in patient subjects) to days

(in healthy control subjects). [27,28] [29] To date however, measurement stability data for 24 hour re-assessment of healthy control participants is lacking.

Findings from the current study reveal statistically (but not clinically) significant improvement in DVA performance under well rested conditions that may be consistent with a mild practice effect.[38] The magnitude of DVAT improvements in this study (2-3 optotypes) in response to yaw and pitch plane impulses are similar to previously reported results in both healthy control and patient subjects.[27-29] In separate studies, Herdman and Schubert reported enhanced DVA performance for same day re-assessments in patients with change magnitudes of 2.3 $\pm$ 0.7 optotypes (yaw) and 2 optotypes (pitch) respectively. [27,28] Mohammad and colleagues reported small but significant yaw DVA improvements in patients with vestibular disorders for same-day and 7-day re-assessments. [29] Mean yaw change magnitudes in the Mohammad et al study ranged from of 0.04 $\pm$ 0.03 to 0.07 $\pm$ 0.01 LogMAR though pitch performance remained consistent. [29]

Test-retest reliability estimates of the DVAT in this study were lower than those previously reported by Herdman, Schubert and Mohammad. [27,29,30] This finding is most likely a function of the limited variability in the DVA data and a consequent violation of the restriction in range assumption for the ICC model.[38] It is well established that a restriction in the range of normally distributed values can reduce correlations in ICC models causing artificially deflated reliability estimates.[38,39].[40] Statistical theory indicates that when *within* subjects variance in a model is greater than *between* subjects variance, as was confirmed by post hoc ANOVA reported in the results of this study, the reliability estimate may not be considered valid because the actual limits of the ICC do not match the theoretical limits of 0.00 to 1.00.[38,41] The lack of between subjects variance observed in the model is consistent with sample homogeneity in the two key

variables known to affect DVA performance: participant age and vestibular function. In contradistinction with significant participant age variability reported by Herdman and Schubert (both assessed DVA performance in control and patient participants across multiple decades), these data reflect performance in a sample with a mean age of 21.7 $\pm$ 3.3 years. Violation of the restriction in range assumption in this case seems plausible given the extent to which DVA performance is known to vary with age. [27,28]

Restricted range was also evident in the DVAT performance data. This is not however surprising given that participants in the current study reported no history of head trauma or vestibular pathology and demonstrated normal vestibular responses to head impulse testing. Conversely, participants in previous DVA investigations demonstrated significant performance variability reflecting a much broader range of vestibular function than was observed in this study. Herdman and colleagues for example, reported DVA performance across a diverse sample with responses ranging from normal (0.043 + 0.048) in healthy controls aged 19-79, and subtly impaired (0.286 + 0.144 or ~ 20/40) in patients with unilateral vestibular loss, to more significantly degraded DVA (0.397 +0.137 or ~ 20/50) in patients with bilateral vestibular hypofunction. [27]

The relatively small sample size may have also adversely influenced reliability and ICC confidence interval estimates. Portney and Watkins indicate that for cohorts less than n=30, sampling distributions tend to be flatter than normal and ICCs tend to be less precise resulting in wider confidence intervals. [38] The current study reported DVA performance in a cohort of 20 participants; a number far exceeded by sample sizes in both the Herdman (n= 97) and Schubert (n= 64) studies.[27,28]

Though the reliability findings from this study are admittedly suspect given the homogeneity of the sample, the observation that passive DVA testing seemed to yield superior repeatability to active testing suggests a potentially interesting consideration for gaze stability assessment. It is possible that superior DVA reliability may be achieved under passive testing conditions when impulses are administered by an experienced clinician given an examiner's superior and consistent control of the magnitude, timing, and velocity of head movement stimuli relative to active DVA testing. Future research should explore potential reliability differences between active and passive testing approaches. In summary, despite the questionable ICC scores and CIs reported on these data, the relatively small overall magnitude of DVA change demonstrated by participants in this and previous studies suggests that the DVAT is sufficiently stable to serve as an acute screening tool for concussion related vestibular dysfunction in a deployed environment.

Yaw DVA and Sleep Deprivation

Results of this study yielded no statistically or clinically significant change in yaw DVA following 26 hours of sleep deprivation. These findings suggest that functional gaze stability is preserved following short term sleep deprivation under head movement and illumination conditions characteristic of daily activities. Consequently, these data provide preliminary support for the use of high-energy, functional techniques like DVA to assess gaze stability in conditions where sleep deprivation may confound assessment.

Results from this study reveal potential differences between moderate- and high- velocity assessment techniques that clinicians should consider when selecting and interpreting objective measures for patients with traumatic dizziness. Possible explanations for divergent findings

between this study and that performed by Quarck et al include differences in rotational stimulus characteristics and experimental lighting conditions. [24]

Head Movement Stimulus Characteristics

Evidence suggests that vestibular responses in human and non-human primates are frequency- and velocity- dependent meaning that aVOR response magnitudes vary depending upon the kinematic parameters of the rotational head movement stimuli applied.[42,43] Specifically, physiological data in primates support the idea that the vestibular system is capable of generating non-linear aVOR responses to rapid, high-frequency component angular head movements in order to stabilize gaze during highly dynamic (i.e., high velocity, high frequency) activities such as walking or running.[43,44] Though peak rotational head velocity and acceleration were not measured in this study, head impulses performed during DVA testing are known to approach 3500°/s^2 and 250 °/s, values which greatly exceed the moderate acceleration (100 °/s^2) and velocity (60 °/s) stimuli applied by Quarck and colleagues.[24,33,45] We suggest that the "high energy" head movement stimuli applied during DVA testing in this study may have contributed to the well preserved gaze stability performance observed among study participants.

Other studies measuring aVOR function have yielded similar results.[32,46] High- velocity, acceleration, and frequency component rotations are known to generate gains at or close to 1.00 (a perfectly compensatory response).[32,46] A gain of 1.00 implies that there is precise agreement between head movement and eye movement such that the object of one's interest is clear and stable on the fovea.[3] Conversely, a gain of greater than 1.00 implies that eye velocity actually over-compensates for head velocity which can degrade gaze stability.[3] In the Quarck et al study, initial (rested) mean VOR gain values were initially measured at 0.77 ± 0.16 in response to rotational stimuli of 60 °/s and 100 °/s^2 increasing to a gain of 0.90 ± 0.18 after sleep

deprivation.[24,42] One possible explanation for the different responses to sleep deprivation between "high" and "moderate" energy stimuli may be that an "optimized" system (i.e., stable gaze characterized by a gain of ~ 1.00 or DVA not significantly different from SVA) may demand little descending drive (from the tempoparietal junction) whereas a system not so primed may require a stronger descending signal. Given this explanation, an optimized vestibular system, would actually need to suppress descending inputs to avoid excessive aVOR "augmentation" that would be functionally *detrimental* to sensory stability.[4,43,44] Thus, while it is possible that sleep deprivation affects gaze stability differently with moderate head movement stimulation relative to higher energy impulses, additional investigation on this topic will be necessary better characterize the relationship between head movement kinematics and aVOR responses following sleep deprivation.

Experimental Lighting Conditions

DVA testing in this study was performed under well-lit laboratory conditions to ensure optimal viewing of the visual stimulus. If the enhanced aVOR response to rotational step testing in the Quarck et al study was precipitated solely by the unexpected nature of the stimulus as the authors suggest, one might have anticipated a similar augmentation of DVA in the current study sample following sleep deprivation in response to passive head impulses.[24] Results of this study did not reveal this, a finding possibly related to the presence of visual fixation during DVA test conditions. It is possible that because participants were well aware of their visual surroundings at all times during the DVA protocol (to include passive impulses), there was little or no demand on the tempoparietal junction to re-establish orientation as there presumably was with fixation

removed during rotational chair testing in the Quarck study.[24] aVOR function is known to be enhanced in well-lit conditions relative to performance measured in the dark.[3,47]

Pitch DVA and Sleep Deprivation

Pitch plane DVA measurements obtained following 26 hours of sleep deprivation revealed a mean degradation in visual acuity equivalent to less than one line on a standard Snellen eye chart. Deterioration of vertical visual acuity was found to be statistically but not clinically significant.[28] While it is unlikely that observed changes reflect disruption of descending cortical influences, (given the absence of corresponding significant disruption to yaw plane responses and common central pathways), the subtle decrement in pitch DVA could be related to increased blink-related impediments to visual acuity.

Increased blink frequency or central perseveration of the blink response due to central fatigue and decreased attention may account for the subtle degradation in observed vertical DVA. In one study investigating the effect of 20 hours of sleep deprivation on normal subjects, researchers reported that participant *blink rate* was significantly higher after a night without sleep than before.[48] Complementary findings in flight experiments reveal that increases in blink rate are closely associated with degraded performance under conditions that necessitate gaze shifting (i.e., saccades) or head movement - behaviors which are both characteristic of DVA testing.[45,49] Other authors have suggested that like blink frequency, blink *closure time* (i.e. central perseveration of the blink response) increases with increasing time on task when fatigued. This too might have adversely affected pitch DVA performance.[49,50]

While the DVA metric used in this study precludes a description of eye movement kinematics or the verification of blink behavior, there is evidence of increased blink frequency in the human factors literature following sleep deprivation using both scleral search coil and infrared camera technology.[51,52] Pitch plane head impulses have also been shown to elicit more frequent blinks than yaw plane rotations as measured with wireless scleral search coil during a gaze stabilization task.[2] Given that accurate performance on the DVAT necessitates *visualizing* a target to discriminate optotype orientation; the hypothesis for fatigue mediated DVA degradation could describe subtle differences in visual acuity noted in this study. Increased frequency and longer duration of blinks would both account for subtly diminished gaze stability during pitch plane head movements without implicating "abnormal" VOR performance in a group with no known history of vestibular dysfunction or head injury and better than 20/20 DVA in all tested conditions.

Study Limitations

As discussed, reliability values in this study were lower than previously reported in the rehabilitation literature.[27-29] While this discrepancy could be related to variability in equipment or possible differences in DVA system resolution, it seems most likely that low ICCs were the result of a restriction in the DVA data range given the lack of variability in our young, healthy control sample.[38,39] Previous clinical studies using DVA as an outcome measure have consistently demonstrated a broader range of LogMAR scores given the presence of pathologically high DVAT scores from patient subjects with unilateral or bilateral vestibular loss. [27-29] It is probable that DVAT reliability would have been superior in a more heterogeneous sample however, the small DVA change magnitudes observed during reliability testing in this and earlier studies suggest that this measure is sufficiently stable for use in austere

environments to screen concussed Service Members for vestibular co-morbidity and to help guide RTD decision making.[27-29]

Conclusion

Our findings suggest that 26 hours of sleep deprivation does not have a significant effect on dynamic visual acuity in healthy control Service Members. Data reveal that changes in DVA under both rested and sleep deprived conditions were within accepted and published ranges of normal variability for this measure. Further well-controlled investigations of head movement stimulus characteristics in patients with vestibular disorders will be essential to better characterize the relationship between sleep deprivation and gaze stability.

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Table 1. Yaw DVA: Intraclass correlation coefficients (3, 1); (95%CIs)

	A_L_2	A_R_2	P_L_2	P_R_2
A_L_1	.020 (-.416 to .449)			
A_R_1		.144 (-.308 to .543)		
P_L_1			.541 (.141 to .789)	
P_R_1				.409 (-.029 to .715)

A = Active; P = Passive; R = Right; L = Left; 1 = 1st Trial; 2 = 2nd Trial

Table 2. Pitch DVA: Intraclass correlation coefficients (3, 1); (95%CIs)

	A_D_2	A_U_2	P_D_2	P_U_2
A_D_1	.299 (-.154 to .648)			
A_U_1		.325 (-.126 to .664)		
P_D_1			.522 (.115 to .779)	
P_U_1				.613 (.245 to .826)

A = Active; P = Passive; D = Down; U = Up; 1 = 1st Trial; 2 = 2nd Trial

Table 3a Absolute Yaw DVA Values

Time	Active Yaw_Left (SD)	Active Yaw_Right (SD)	Passive Yaw_Left (SD)	Passive Yaw_Right (SD)
T1 (T – 24 Hours)	-0.195 (0.09)	-0.175 (0.08)	- 0.175 (0.12)	-0.205 (0.09)
T2 (T = 0 Hours)	-0.225 (0.07)	-0.235 (0.07)	-0.230 (0.08)	-0.235 (0.09)
T3 (T + 26 Hours)	-0.225 (0.08)	-0.240 (0.08)	-0.215 (0.12)	-0.205 (0.11)

Table 3b Absolute Pitch DVA Values

Time	Active Pitch_Up (SD)	Active Pitch_Down (SD)	Passive Pitch_Up (SD)	Passive Pitch_Down (SD)
T1 (T – 24 Hours)	-0.240 (0.07)	-0.225 (0.06)	-0.265 (0.06)	-0.235 (0.17)
T2 (T = 0 Hours)	- 0.280 (0.05)	-0.245 (0.07)	-0.28 (0.05)	-0.27 (0.05)
T3 (T + 26 Hours)	-0.225 (0.08)	-0.245 (0.07)	-0.265 (0.08)	-0.24 (0.09)

Figure 1. Change in mean group Yaw DVA values from T1 to T2 (Test- retest stability) were obtained under rested conditions. Change in mean group Yaw DVA values from T2 to T3 reflect 26 hours of supervised sleep deprivation (Sleep deprivation protocol). Active DVA values are presented with solid line and passive DVA is stippled. Error bars characterize the collective variance (standard deviations) for measurements at each time point. The Snellen Eye Chart equivalent scores follow the LogMAR score in parenthesis. Note visual acuity is better than 20/20 in all cases. Statistical significance of time effect is denoted with open bracket ($p = 0.0004$). As a point of reference please note that functional yaw plane DVA deficits in patients with Vestibular Hypofunction have been measured in the range of LogMAR= 0.3 - 0.4 per the findings of Herdman et al 2003.

Figure 2. Change in mean group Pitch DVA values from T1 to T2 (Test- retest stability) were obtained under rested conditions. Change in mean group Pitch DVA values from T2 to T3 reflect 26 hours of supervised sleep deprivation (Sleep deprivation protocol). Active, down directed head impulses are depicted with the thin solid line; passive, down impulses with the stippled line; active upward directed impulses with the bold solid line; and passive upward directed impulses with the stipple-circle line. Error bars characterize the collective variance (standard deviations) for measurements at each time point The Snellen Eye Chart equivalent to the LogMAR score is depicted in bold below. Note visual acuity is better than 20/20 in all cases. Statistical significance of time effects are denoted with open brackets. As a point of reference please note that functional yaw plane DVA deficits in patients with Vestibular Hypofunction have been measured in the range of LogMAR= 0.3 - 0.4 per the findings of.Schubert et al 2002.

Figure 1.

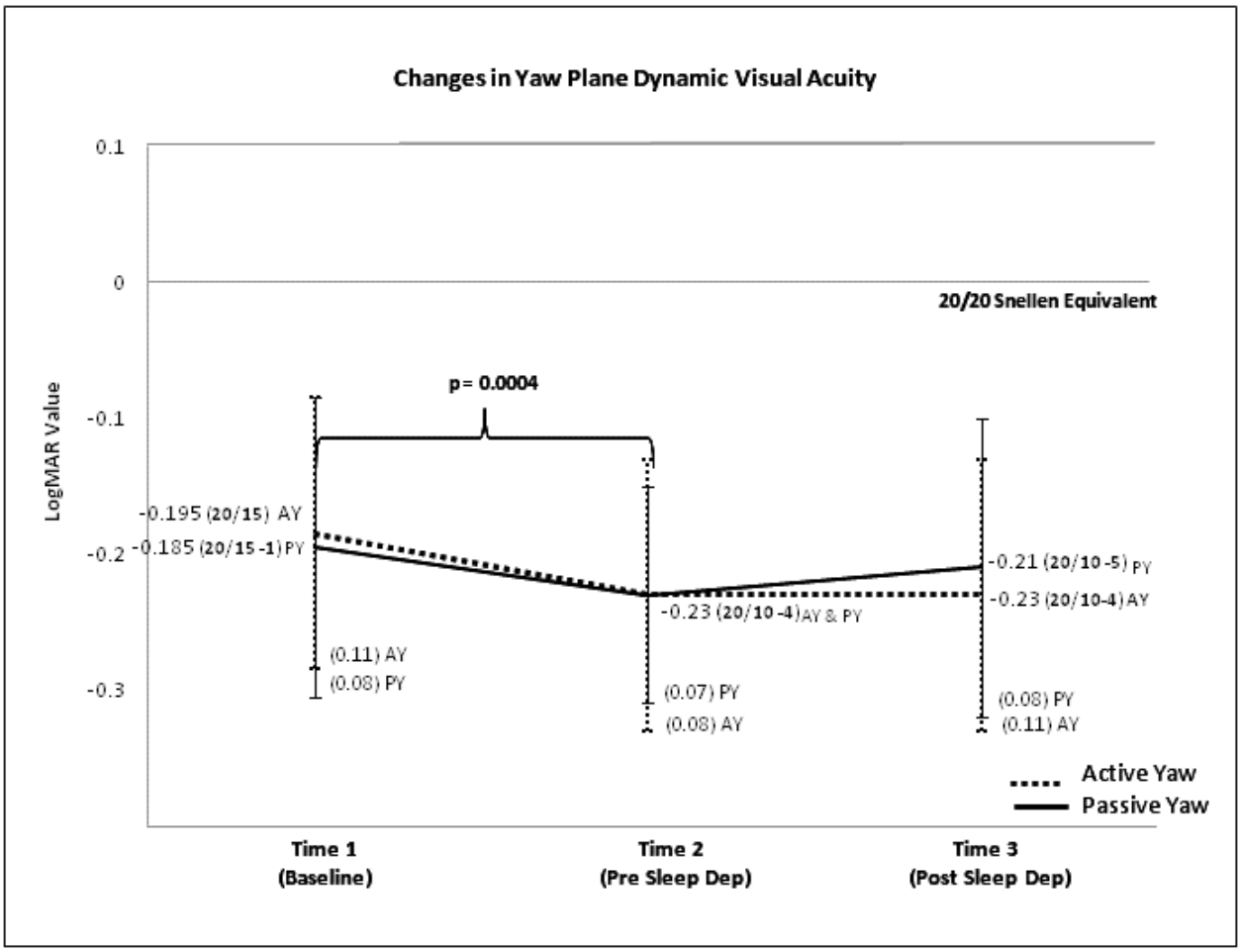
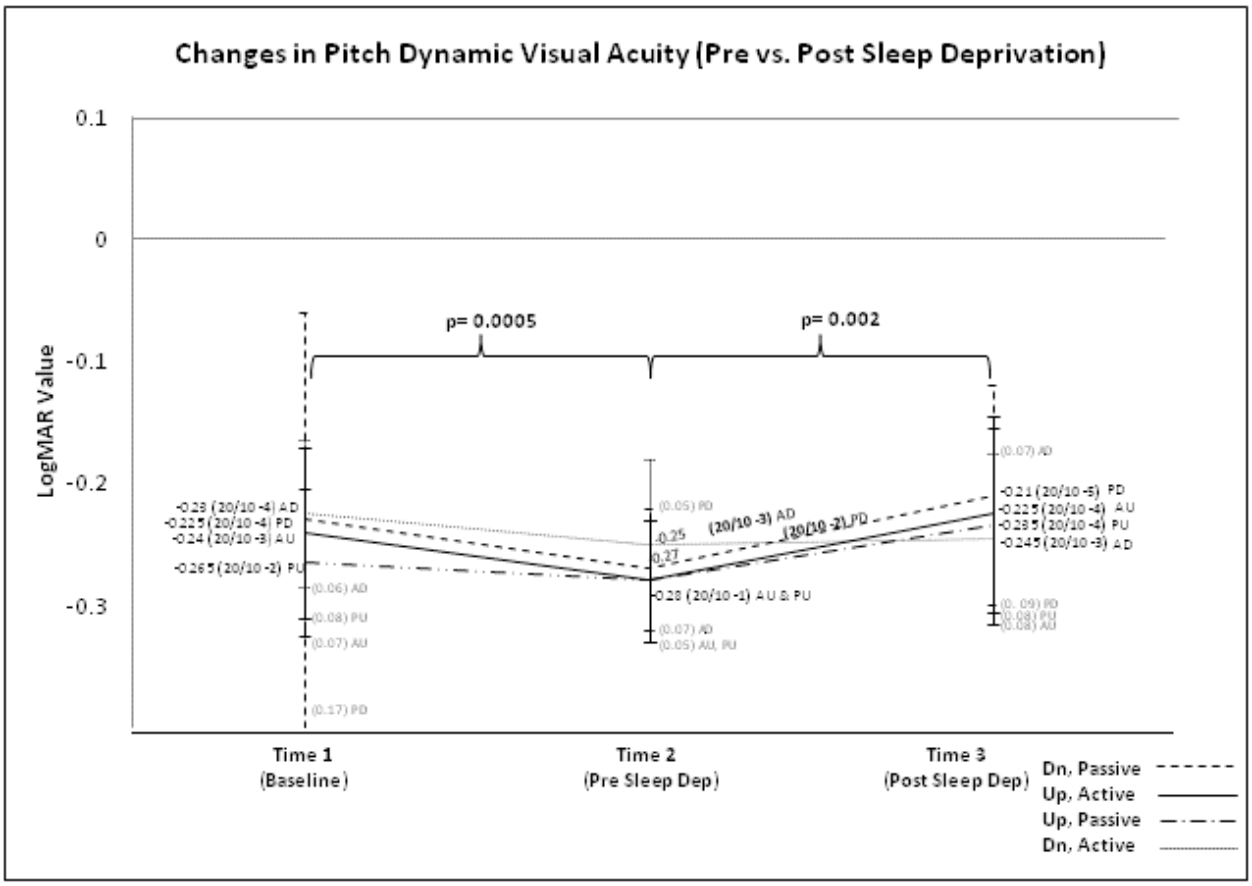


Figure 2.



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Sleep Deprivation Has No Effect on Dynamic Visual Acuity in Military Service Members Who Are Healthy

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Dynamic visuomotor synchronization: Quantification of predictive timing

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Abstract When a moving target is tracked visually, spatial and temporal predictions are used to circumvent the neural delay required for the visuomotor processing. In particular, the internally generated predictions must be synchronized with the external stimulus during continuous tracking. We examined the utility of a circular visual-tracking paradigm for assessment of predictive timing, using normal human subjects. Disruptions of gaze–target synchronization were associated with anticipatory saccades that caused the gaze to be temporarily ahead of the target along the circular trajectory. These anticipatory saccades indicated preserved spatial prediction but suggested impaired predictive timing. We quantified gaze–target synchronization with several indices, whose distributions across subjects were such that instances of extremely poor performance were identifiable outside the margin of error determined by test–retest measures. Because predictive timing is an important element of attention functioning, the visual-tracking paradigm and dynamic synchronization indices described here may be useful for attention assessment.

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Introduction

Visual tracking supports perceptual stability of the object of interest that is in motion. When visually tracking a moving target to maintain its image on the fovea, spatial and temporal predictions are used to circumvent the neural delay required for the visuomotor processing. In particular, the internally generated predictive drive must be synchronized with the external stimulus during continuous tracking, which highlights an important distinction between being able to predict *that* a target will appear at a specific location and being able to predict *when* that event will occur. Accurate predictive timing is the ability to synchronize what is expected with what is observed, which is considered to be a function of attention (Ghajar & Ivry, 2008). Therefore, we investigated whether a visual-tracking paradigm can be used to assess an individual's capacity for predictive timing. A circular visual-tracking paradigm (Umeda & Sakata, 1975; van der Steen, Tamminga, & Collewijn, 1983), with the target traveling at a constant angular velocity with a fixed radius from the center, has a special advantage in that both the spatial and temporal aspects of the target motion are highly predictable. This movement can continue indefinitely within the orbital range of the eye, which makes the stimulus particularly suitable for studying dynamic gaze–target synchronization during predictive visual tracking.

Despite the recent advances in elucidating the neural circuits that convey the visual information to generate pursuit eye movements (see Orban de Xivry & Lefevre, 2009), the precise localization and interrelationships of the neural substrates for the extra-retinal, cognitive components of visual tracking have yet to be determined. However, it is generally assumed that the substrates for these components

are broadly distributed; thus, even a subtle neurocognitive dysfunction could impair visual-tracking behavior. Abnormalities in visual-tracking behaviors have been associated with various psychiatric (Diefendorf & Dodge, 1908; Iacono & Lykken, 1979; Lipton, Levin, & Holzman, 1980) and neurologic (Bronstein & Kennard, 1985; Morrow & Sharpe, 1995; White, Saint-Cyr, Tomlinson, & Sharpe, 1983) disorders, brain lesions (Lekwuwa & Barnes, 1996a, 1996b), and pharmacological effects (Blekher, Miller, Yee, Christian, & Abel, 1997; Rothenberg & Selkoe, 1981).

Using videooculography, eye movement can be monitored easily, precisely, and continuously. Furthermore, oculomotor paradigms are resilient to inconsistent or poor subject effort (Heitger et al., 2009). However, to evaluate specific visual-tracking abnormalities in a quantitative manner, characterization of normal behavior using a well-defined testing paradigm is necessary. Visual-tracking performance should then be objectively quantified using standardized parameters such as smooth pursuit velocity gain, phase error, and root-mean-square (RMS) error. Impairments in visuomotor synchronization may also be assessed by variability of gaze positional error relative to the target (Maruta, Lee, Jacobs, & Ghajar, 2010; Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010).

Our interest in developing a rapid assessment of attention in concussion patients has led to the use of a circular visual-tracking paradigm (Maruta, Lee, et al., 2010; Maruta, Suh, et al., 2010). The diagnosis of concussion, or mild traumatic brain injury (TBI), is made difficult by symptoms that are often subtle and transient. Although impaired attention is a hallmark of TBI (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Stuss et al., 1989), the impairment can go undetected by traditional neurocognitive measures that rely on verbal or motor responses to discrete stimuli and are sensitive to subject motivation and effort.

The use of a visual-tracking paradigm for attention assessment is based on the hypothesis that attention impairments in concussion patients are a consequence of reduced efficacy of predictive timing (Ghajar & Ivry, 2008). Our approach is supported by the evidence that eye movement and attention processes are implemented by closely overlapping areas of the brain (Corbetta et al., 1998) and that attention is required during visual tracking (Baumann & Greenlee, 2009; Chen, Holzman, & Nakayama, 2002). Our previous study of circular visual tracking in concussed patients suggested that impaired predictive timing, rather than disengagement from prediction, can result in poor tracking (Maruta, Suh, et al., 2010). This study also supported that impaired visual-tracking performance was related to injury of attention-related anatomical locations and diminished neurocognitive performance.

The primary goal of this study is to describe the indices and normal variations of dynamic visuomotor synchronization during circular visual tracking in healthy, young adult subjects, from which the criteria for abnormal performance can be derived. In addition, because the clinical utility of a test is ultimately limited by the reliability of its measurements, we aim to establish the test–retest reliability of the visual-tracking measures.

Method

The present study, utilizing a prospective, repeated measurement design, was conducted at the United States Army Research Institute of Environmental Medicine (USARIEM) located at the Natick Soldier Center, Natick, MA, as part of a clinical research award to Brain Trauma Foundation, New York, NY. The protocol was reviewed and approved by the USARIEM Human Use Review Committee and the USARIEM Office of Research Quality and Compliance. Written informed consent was obtained from all subjects prior to data collection.

Subjects

The subjects in this study were military volunteers recruited for a larger ongoing study of the effects of sleep-deprivation-induced fatigue on neurocognitive function. The visual-tracking data presented in this report were collected during two test sessions separated across a 14-day interval while subjects were rested. Both sessions took place in the morning (0630–0930) in order to control for the circadian effects and to coincide with subjects' typical morning schedules.

Potential subjects were recruited via scheduled, in-person briefings. Eligibility criteria included having no prior history of head injury with loss of consciousness, no substance abuse problems/treatment, no known neurological disorders, no major psychiatric disorders (including attention deficit hyperactivity disorder [ADHD]), and no gross visual (no worse than 20/30 corrected or uncorrected) or hearing problems. Participation was limited to men and women 18–50 years of age who had completed at least 12 years of education and were able to abstain from caffeine use for at least 26 h. Prospective subjects underwent a structured screening interview conducted by a member of the research staff. This screening interview consisted of the Conners Adult ADHD Rating Scale–Self-Report: Short Version (CAARS–S:S; Pearson, San Antonio, TX), the Post Traumatic Stress Disorder (PTSD) Checklist–Civilian Version (PCL–C; National Center for PTSD, U.S. Department of Veterans Affairs), the Center for Epidemiologic Studies Depression Scale (CES–D; Radloff, 1977), and the Brain Injury Screening Questionnaire (BISQ; Gordon, Haddad, Brown, Hibbard, & Sliwinski, 2000). Exclusion criteria consisted of a *t*-score of >70 on the CAARS–S:S or a positive result for brain injury on the BISQ. Family history of psychiatric disorders was not assessed.

A total of 50 subjects were enrolled in this study. Three subjects withdrew from the study after enrollment because of scheduling conflicts. Demographic information for the remaining 47 subjects is presented in Table 1.

Eye movement recording

The visual-tracking protocol was implemented on an apparatus that integrated stimulus presentation and eye tracking (EyeLink CL, SR Research, Ontario, Canada). Prior to testing, an eye chart was used to verify that the subject had normal or corrected-to-normal vision. The subject was seated in a normally lit room with the head stabilized using a head- and chinrest during testing. The visual stimulus was presented using a 120-Hz frame rate LCD monitor (Samsung SyncMaster 2233RZ; see Wang & Nikolić, 2011) placed 47.5 cm from the subject's eyes. The monitor area subtended 53° (horizontal) by 35° (vertical) in visual angles with a resolution of 0.033°/pixel. Movements of both eyes were recorded under binocular viewing conditions with a sampling frequency of 500 Hz with a single desktop camera while the subject's face was illuminated with an array of infrared LEDs.

The test stimulus consisted of a red circular target, 0.5° diameter in visual angle with a 0.2° black dot in the center. The target moved in a circular clockwise trajectory of 10° radius at 0.4 Hz against a black background, with the target speed corresponding to 25°/s. The stimulus fell in the frequency range within which progressive degradation of performance occurs in normal subjects (Barnes, 2008).

Table 1 Subject demographics

	Mean	*SD*
Age (years)	21.2	3.5
Education (years)	12.5	1.2
Time active in army (months)	9.1	3.4
CAARS–S:S Index	40.0	7.0
PCL–C total score	21.3	5.9
CES–D total score	5.9	4.7
	N	Percentage
Gender		
Male	35	74.5
Female	12	25.5
Ethnicity		
White (Caucasian)	24	51.1
Black (African-American)	12	25.5
Hispanic or Latino	10	21.3
Other	1	2.1
Rank		
Private	1	2.1
Private II	32	68.1
Private First Class	12	25.5
Specialist	2	4.3

The testing sequence lasted approximately 5 min and consisted of a practice run, calibration, and two consecutive recorded test runs. Standardized instructions for completion of the test were presented both visually on the computer monitor and aurally via the attached audio speakers. Additional audio cues (such as "beeps" and "clicks") were provided to facilitate the testing process. No audio cue was provided during the tracking task, however. Although largely automated, the testing protocol required intervention by the experimenter to enter relevant information, adjust the camera, and initiate the calibration procedure.

Calibration of the eye position was conducted by having the subject fixate on a target presented at eight locations on the circular path of the test stimulus and one additional fixation point at the center of the circular path. The fixation target was presented at these nine locations in a randomized order. When an error was suspected or detected at any location, the target was presented there again. The calibration was validated by presenting the fixation target at the nine locations in a similar fashion.

The practice run included two cycles of circular target movement identical to the subsequent test runs except in the number of cycles. Each of the two test runs consisted of six cycles of circular movement corresponding to 15 s in duration per test run. With both practice and test runs, the target was presented at the central location to serve as a visual fixation point prior to and following the circular movement of the target. The instruction for the tracking task was "follow the movement of the target as closely as possible." Target analysis, which is known to improve visual-tracking performance (Holzman, Levy, & Proctor, 1976; Shagass, Roemer, & Amadeo, 1976; Van Gelder, Lebedev, Liu, & Tsui, 1995), was not part of the testing procedure.

Eye movement analysis

Eye movement data were analyzed using a custom MATLAB program (The MathWorks, Natick, MA, USA). As described below, a single set of performance indices was obtained for each testing session that included two brief repeated test runs, although between-trial variations were also considered. The eye and target positions were expressed in visual angle. Blinks and other events during which the pupil was occluded were identified by the computer program and excluded from further analyses. To compensate for any potential artifact caused by unwanted head drifts relative to the camera during eye movement recording, the differences between the recorded gaze positions and the central fixation point presented before and after the circular target movement were calculated. The offset in the horizontal and vertical eye positions caused by a head drift was

estimated with a linear interpolation between the pre- and post-run fixation differences and digitally subtracted from the data. In practice, however, the drift measured during each 15-s trial had an average of 0.50° in total visual angle with a standard deviation (*SD*) of 0.49°; thus, a correction would have been unnecessary in most cases.

To visualize gaze positional errors relative to the target motion, the target position was expressed in polar coordinates, and both the target and eye positions were rotated so that the target was at the 12 o'clock position (Fig. 1b). In this reference frame, the distance between the origin and the gaze represented the instantaneous radius of the gaze trajectory, and the angle formed by the vertical axis and the gaze vector represented the phase difference between the target and the gaze—that is, phase error. Positive phase error was defined as the gaze leading the target.

We quantified intraindividual variability in visual-tracking behavior using the *SD* of gaze positional errors relative to the target (Maruta, Suh, et al., 2010). The variability in the radial direction was measured with the *SD* of gaze errors perpendicular to the target trajectory, whereas the variability in the tangential direction was measured with the *SD* of gaze errors along the target trajectory. To facilitate comparison, the error variability measures were expressed in visual angle for both the radial and tangential directions. The radial error corresponds to the deviation in the radius of the gaze trajectory from the circular trajectory of the target, and the tangential error is proportional to the phase error.

Horizontal and vertical eye position data were two-point differentiated to obtain eye velocity, which was smoothed with a ten-point moving average filter. The signal was further differentiated to obtain eye acceleration, which was smoothed with a five-point moving average filter. Saccades were detected with velocity and acceleration thresholds of 100°/s and 1,500°/s^2, respectively, and the saccade segments in the velocity data, which were expressed as sharp spikes, were replaced with straight lines connecting the ends of the remaining segments. The saccade detection thresholds took into consideration that saccades were generated during pursuit rather than fixation. Eye position and velocity traces were visually displayed by the analysis program, and the accuracy of saccade detection was verified.

To measure the level of accuracy in matching the eye velocity to the target velocity, smooth pursuit velocity gain was computed. The amplitudes of horizontal and vertical velocity modulations were obtained by fitting the desaccaded velocity traces with sine curves of the frequency of the circular movement of the target, using fast Fourier transformation. The fitted traces were overlaid on the eye velocity traces in the software interface and visually matched with the smooth pursuit velocity modulations. Horizontal and vertical gains were the ratios between the amplitudes of the respective components of eye and target velocities.

To obtain a metric equivalent to the combination of horizontal and vertical smooth pursuit gain, phase error data were two-point differentiated and smoothed with a ten-point moving average filter. Instantaneous angular velocity gain was expressed as unity plus the ratio of phase error velocity to the constant angular velocity of the target. Average smooth pursuit angular velocity gain was then calculated by excluding saccade segments.

To measure the level of positional precision of visual-tracking performance in horizontal and vertical directions, RMS positional deviations of the gaze from the target were calculated for the respective directions. The *SD*s of radial and tangential errors, mean phase error, angular smooth pursuit gain, and RMS errors were computed from the combination of the two test trials included in each test sequence. The horizontal and vertical gain values were computed for each trial and then averaged. The data segments from the first cycle of each test run were discounted from the analysis so that the transient response to the initial target movement was excluded.

Eye movement was recorded binocularly. A pilot analysis of the day 1 data with Pearson's *r* calculated for the five visual-tracking parameters showed a high correlation between the left and the right eyes (range .90–.99). However, only monocular data were pooled for further analyses. The use of monocular data was based on the following rationale: Generally, small radial error variability provides an indication of spatial accuracy in the recorded data, since it combines the effects of a high level of performance by the subject and accurate eye position calibration. The eye-tracking equipment utilized in this study employed a single camera to record both eyes; thus, the spatial accuracy of eye position calibration in our data may have been compromised by the placement of the camera relative to each eye. To focus on the records that likely better represented the subject's performance, the data from the eye with the smaller *SD* of radial errors were used for further analyses. This routine is justified because ocular dominance may have little relevance to the level of visual-tracking performance (Bahill & McDonald, 1983).

Statistical analysis

Characterization of visual-tracking performance was aided by the following statistical procedures. Pearson's correlation coefficient *r* was computed to determine the level of linear dependence between test–retest measurements and between parameters. A paired *t*-test was used to test against the null hypothesis that no systematic difference existed between measurements (46 degrees of freedom [*df*]). The alpha level was set at $p = .05$. The use of the *t*-test for the test–retest analysis is justified because a single set of performance indices was associated with each testing session. That no significant between-trial effect existed was confirmed using a two-way repeated measure analysis of variance (ANOVA).

The intraclass correlation coefficient (ICC) with one-way random effect model was computed to determine the level of test–retest agreement (Bartko, 1966). ICC ranged from 0 to 1, with the latter value indicating a perfect match. Since the computation of ICC assumes normality of the data and is biased by the skewness of the data, the raw data were transformed with a Box–Cox transformation. The parameter of the transformation was chosen so that the absolute value of the skewness of the distribution of the transformed data was minimized. All measurements except those for mean phase error have positive values. The values for the mean phase error parameter was first offset by a constant value obtained by doubling the minimum (negative) value before the application of the Box–Cox transformation.

In addition to assessing the relative reliability with ICC, the absolute reliability of the visual-tracking test was assessed by analyzing the distribution of test–retest differences defined as the value for the second measurement minus that for the first. When the differences (ΔX) follow a normal distribution, approximately 95 % of ΔX should lie within the mean ± 1.96 *SD*, which constitutes the 95 % confidence interval of repeatability (Bland & Altman, 1986, 1999). This analysis does not assume any specific shape of the distribution of the measurements *X*.

The Bland–Altman method was also used to assess the absolute agreement between smooth pursuit angular velocity gain and combinations of horizontal and vertical smooth pursuit velocity gains. The 95 % confidence interval of the difference was calculated from within-individual test–retest means of these gain parameters.

Results

Performance characteristics

Despite the highly predictable nature of the target movement, visual tracking was generally imperfect. A typical performance is illustrated in Fig. 1. The map of the gaze mimicked the circular path of the target, but variability of the gaze positional error described by the radius was evident (Fig. 1a). When the gaze trajectory was redrawn in a polar coordinate reference frame defined relative to the target (Fig. 1b), variability in gaze position error, tangential (parallel) to the target trajectory, also became evident. The spread in the tangential direction accounted for temporal variability, with the gaze falling ahead (clockwise shift) or behind (counterclockwise shift) the target moving at constant velocity (but fixed at the 12 o'clock position in the figure illustration).

In all subjects, eye position modulation during visual tracking involved a mixture of saccadic and smooth pursuit components (Fig. 1c, d). Accordingly, the eye velocity traces had saccadic spikes superimposed on a smooth sinusoidal modulation (Fig. 1e, f). Most of the large saccadic spikes occurred in the direction of and near the peaks and troughs of the smooth modulation, indicating that these saccades were in the forward direction of the target motion. Consistent with this observation, the phase error trace had a sawtooth waveform with repetitive positive-driving fast components (Fig. 1g). The end points of forward saccades rarely landed in phase with the target and appear to be randomly distributed. The end points of saccades in the radial direction were also inconsistent (not shown); thus, saccades generally did not reduce gaze positional errors to serve corrective functions. The origination points of saccades were similarly inconsistent, apparently suggesting a lack of any threshold for triggering that is associated with positional errors.

The distributions of the visual-tracking parameters were skewed so that most subjects performed with better-than-average accuracy and the range of the distribution was extended by infrequent large deviations (Table 2). Smooth pursuit angular velocity gain was comparable to the combination of horizontal and vertical smooth pursuit gain. The 95 % confidence intervals of the differences from the arithmetic or quadratic means of horizontal and vertical smooth pursuit velocity gains were only 0.006 ± 0.046 and 0.004 ± 0.018, respectively.

To compare the accuracy of horizontal and vertical tracking, the test–retest means of the respective components for gain and RMS errors were plotted for each individual (Fig. 2). The dotted diagonal lines in Fig. 2 represent equivalence between horizontal and vertical components. For the most part, the vertical gain values fell below the diagonal lines (left panel) and the vertical RMS errors above the diagonal lines (right panel), both showing better accuracy in the horizontal direction. The mean horizontal gain was significantly higher than the mean vertical gain (paired *t*-test, *t*-value > 9.55, $df = 46$, $p < 10^{-11}$), and the mean horizontal RMS error was significantly lower than the mean vertical RMS error (paired *t*-test, *t*-value < −6.55, $df = 46$, $p < 10^{-7}$).

Although horizontal tracking tended to be more accurate, there were associations both between horizontal and vertical gains ($r = .85$) and between horizontal and vertical RMS errors ($r = .98$) (Fig. 2). Thus, a poor performer in the horizontal dimension was also a poor performer in the vertical dimension in either the positional or the velocity domain, suggesting interdependence between horizontal and vertical eye movements.

While highly synchronized visual tracking was accompanied by saccades that were usually smaller than 1° of visual angle in amplitude, relative to the moving target, some subjects displayed tracking that featured large forward saccades that exceeded 10° (Fig. 3). When drawn relative to the target position, the trajectories of large saccades and smooth components often took the shape of the chord and the arc of a circular sector, respectively. Although the velocity of the target provides an important drive for the ensuing visual

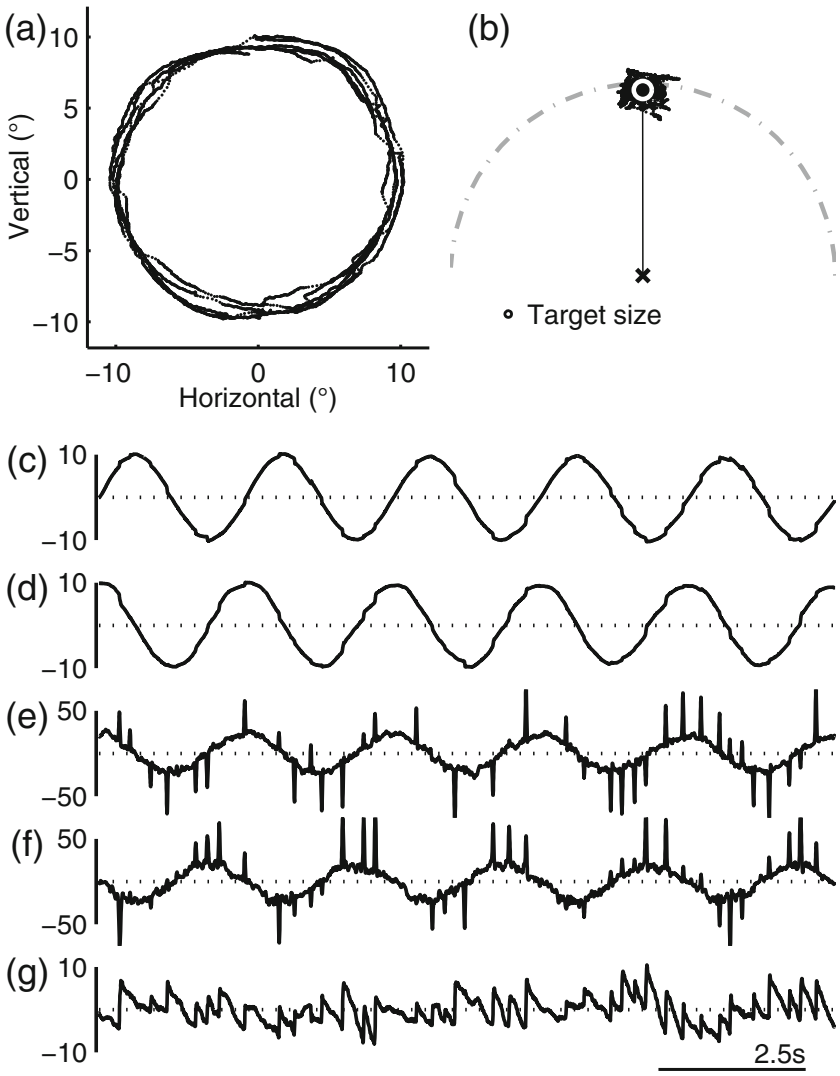

Fig. 1 Typical visual-tracking performance during which a target moved in a circular trajectory of 10° radius at 0.4 Hz (Subject 046). **a** Two-dimensional trajectory of the gaze. **b** Scattergram of gaze positions relative to the target fixed at the 12 o'clock position. The center of the *white circle* indicates the average gaze position. The *dot-dashed curve* indicates the circular path. A proportionally sized target is drawn at the bottom. **c** Horizontal eye position (°). **d** Vertical eye position (°). **e** Horizontal eye velocity (°/s). **f** Vertical eye velocity (°/s). **g** Phase error relative to the target (°). A positive phase indicates lead

Table 2 Test–retest statistics

	SD radial errors	*SD* tan-gential errors	Mean phase	H gain	V gain	Angular velocity gain	RMS_H	RMS_V
Min	0.30°	0.36°	−4.48°	0.26	0.20	0.18	0.28°	0.35°
Max	2.05°	4.92°	17.78°	1.00	1.04	0.98	4.23°	5.62°
Mean Δ	0.03°	0.01°	−0.25°	0.00	0.00	−0.01	0.00°	−0.09°
r	.77	.87	.93	.89	.81	.88	.87	.88
ICC	.68	.63	.64	.75	.71	.76	.67	.62
95 % CI	±0.46°	±0.76°	±2.56°	±0.11	±0.16	±0.12	±0.60°	±0.74°
Mean	0.62°	0.89°	−0.40°	0.88	0.79	0.85	0.66°	0.93°
Median	0.52°	0.66°	−1.15°	0.92	0.82	0.88	0.53°	0.75°
5th worst	0.98°	1.35°	0.35°	0.80	0.65	0.74	1.08°	1.27°
2nd worst	1.68°	3.89°	12.40°	0.69	0.53	0.63	2.62°	2.01°

Top section: Minima and maxima, mean test–retest differences (Δ), and test–retest correlations (Pearson's *r*) of circular visual-tracking parameters, ICC of the respective data set after normalization, and widths of the 95 % confidence intervals of repeatability. Bottom section: Summary statistics of the distributions' within-individual averages

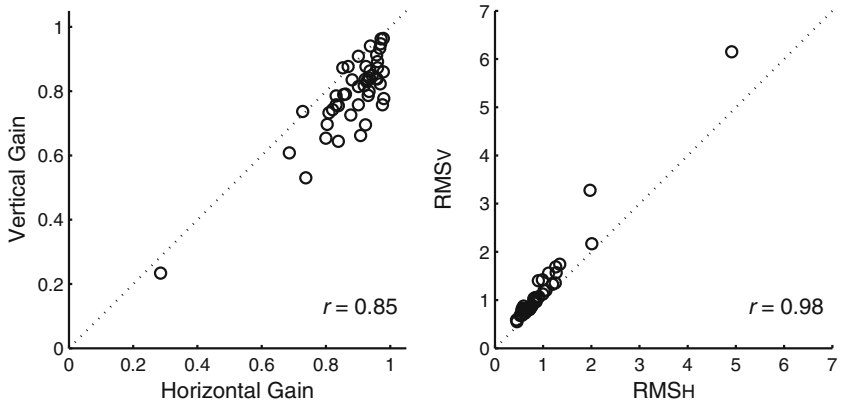

Fig. 2 Relationship between horizontal and vertical tracking. *Left*: Gains. *Right*: RMS errors

tracking, the direction of these large saccades clearly deviated from that of the instantaneous velocity of the target (Fig. 3b–d), which extended along the tangent of the target trajectory (horizontally in Fig. 3). Instead, large saccades anticipated the future path of the target. After landing ahead of the target, the gaze continued to move in the forward direction of the target movement, but at a slower velocity than the target, which slowly brought the gaze position closer to the target.

These large saccades not only caused large gaze positional errors in both radial and tangential directions, but also contributed to an increase in gaze positional error variability in these directions. However, as was noted above, these saccades were anticipatory, and the positional variability was larger in the tangential direction, which is the dimension that accounts for temporal variability. In addition to variability, the presence of large saccades had the effect of driving the mean phase error positive (Fig. 3c, d), because forward saccades in general were repetitive and occurred before there was a substantial lag in the gaze position relative to the target (Fig. 1g).

The presence of large saccades was also linked to low smooth pursuit velocity gain because of the reduced contribution by the smooth pursuit component in the overall tracking. Even so, the simple gain measures could not capture the dynamic interaction of saccade and smooth pursuit components of visual tracking. Similarly, the presence of large saccades was linked to large RMS errors, but the relationship between RMS errors and the tracking dynamics is indirect because RMS errors are sensitive to a phase offset; that is, even a perfect synchrony with a constant phase would yield a large error value. Therefore, although smooth pursuit gains and RMS positional errors are good measures for characterizing the overall accuracy of matching the gaze velocity or position to the target, the *SD* of positional errors in the tangential direction and mean phase error are better suited for characterizing the temporal dynamics of visuomotor synchronization.

Measurement reliability

Any measurement is only an estimate of the true value that represents the subject. The accuracy of such estimates depends on the reliability of the measurement method, which

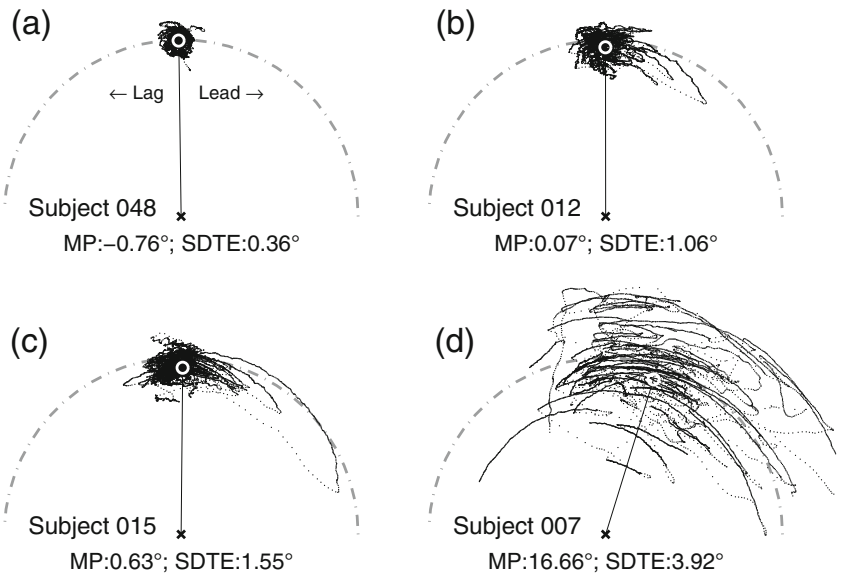

Fig. 3 Different grades of visual-tracking performance. **a**–**d** Increases in positional error variability. The scattergrams follow the same convention as that in Fig. 1b. Each dot corresponds to a sample taken at 500 Hz; consequently, saccade trajectories are represented by series of discrete dots. MP, mean phase error (expressed in phase angle); SDTE, *SD* of tangential errors (expressed in visual angle)

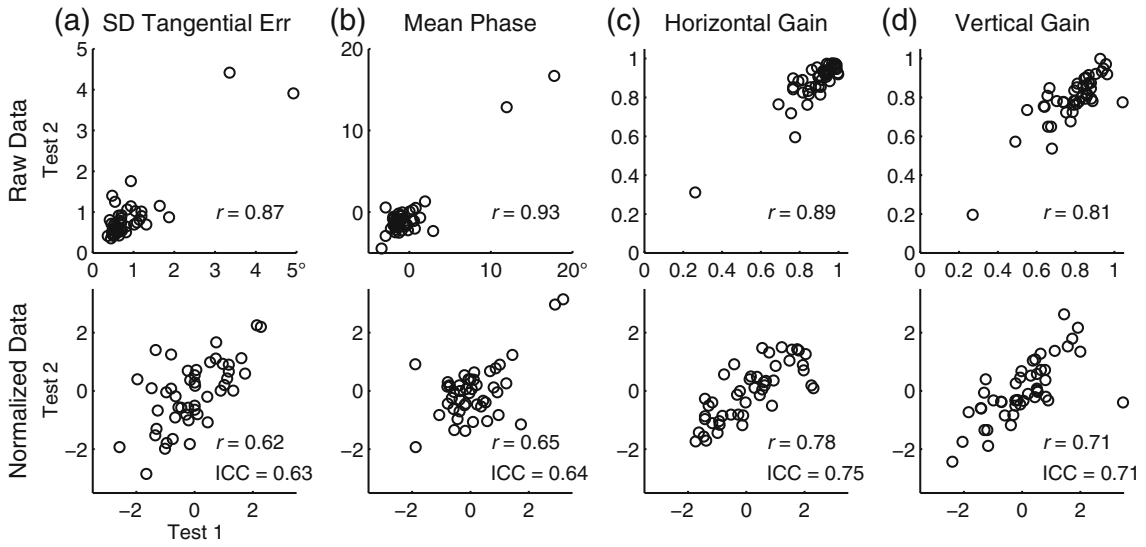

Fig. 4 Test–retest correlograms of raw and normalized data. **a** *SD* of tangential errors. **b** Mean phase error. **c**, **d** Horizontal and vertical gains of smooth pursuit velocity. *Top row*: Raw data. *Bottom row*: Data normalized with Box–Cox transformations and rescaled as *Z*-scores

can be indicated by how closely two measurements taken from each subject agree. Figure 4 shows example test–retest correlations of raw and normalized data. Pertinent statistics for all the visual-tracking parameters we examined are listed in Table 2. The ICC ranged from .62 to .76, indicating moderate to strong test–retest agreement.

To further characterize the reliability of the measurements, within-individual test–retest differences were analyzed. Paired *t*-test did not detect any significant difference between the measurements taken 2 weeks apart (absolute t-value < 1.65, df = 46), and the mean differences were essentially zero (Table 2, mean Δ). A two-way repeated measure ANOVA showed no statistically significant effect of testing session, trial, or interaction in any of the visual-tracking performance indices [test session, $F(1, 46) < 2.94$; trial, $F(1, 46) < 0.37$; interaction, $F(1, 46) < 2.13$]. Therefore, only the variability of test–retest difference was determined to be essential to the analyses of agreement between the measurements from the two test sessions, which can be expressed as the widths of 95 % confidence intervals of repeatability (Table 2). The 95 % confidence interval indicates the range beyond which, given the value of a single measurement, the value of a second measurement from the same subject is unlikely to fall.

Associated with each measurement is a 95 % confidence interval defined about the measured value. The accuracy of the estimate of how a measurement compares in the population in terms of percentile can be evaluated by sliding the 95 % confidence interval along the cumulative distribution plot (Fig. 5). Since percentile values changed rapidly relative to the change in the measured values among high- and average-level performances, the ranges covered by the 95 % confidence intervals in these regions encompassed a large portion of the subject population. Thus, the ability of the visual-tracking test to differentiate high- and average-level performances was low. On the other hand, the individuals represented at the long tail of the distribution stood apart from the majority. The values for the worst two performers were outside the 95 % confidence interval around the median value in all of the visual-tracking parameters (Table 2).

Discussion

In this study, we described a method and indices for characterizing predictive timing using a circular visuomotor synchronization paradigm. The use of circular target motion provided spatial and temporal information of visuomotor prediction. The continuous circular paradigm also precluded the limits on the timing and amplitude of anticipatory saccades imposed by end points that exist in a one-dimensional tracking paradigm (Van Gelder et al., 1995). In addition to some of the standard measures, such as smooth pursuit velocity gain, phase error, and RMS error, we measured the variability of gaze positional error relative to the target. Quantifying performance variability is essential since a dysfunction in predictive timing should increase performance variability. Positional error variability is a useful index in concussion studies since TBI is known to increase intra-individual performance variability on visuomotor tasks (Robertson et al., 1997; Stuss et al., 1989).

Although our subject cohort was limited to healthy enlisted soldiers with similarities in age, training, and physical conditioning, the spatial and temporal accuracy of prediction varied among the subjects. However, the intraindividual test–retest measurements that were taken 2 weeks apart were strongly correlated. Such stability over time suggests that

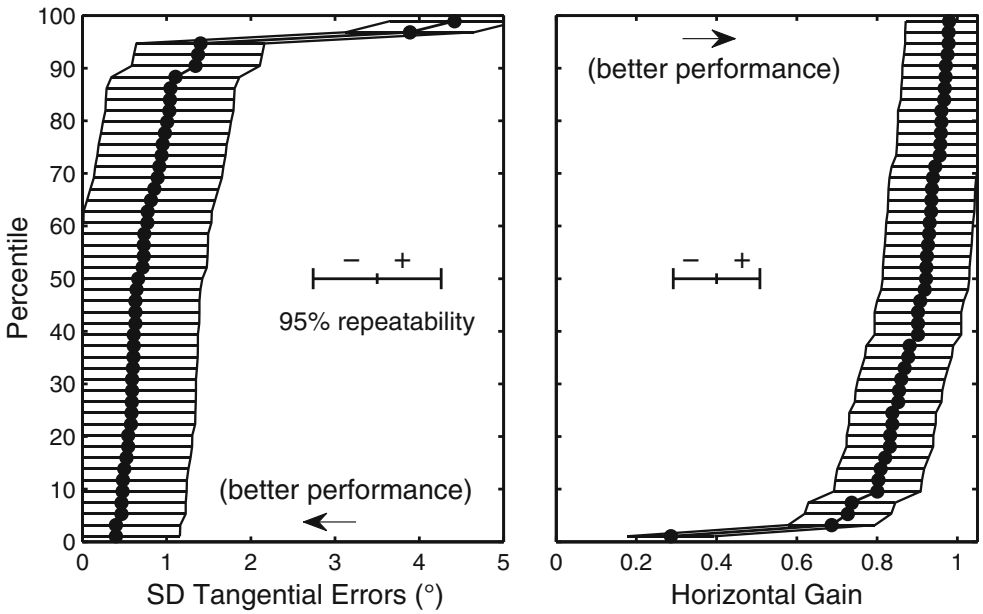

Fig. 5 Cumulative distributions of visual-tracking parameters. *Left*: *SD* of tangential errors. *Right*: Horizontal gain. Each *filled circle* represents a subject. The *scale bars* indicate the 95 % confidence interval of repeatability

interindividual variations in visual-tracking performance are based on neurological differences. These variations in visual-tracking performance should provide insight into the spectrum of cognitive functioning between individuals. Furthermore, a change in visual-tracking performance within an individual may indicate a change in the person's neurological state.

Accuracy of spatial prediction

Visual tracking was more accurate in the horizontal than in the vertical direction. This finding is consistent with previous reports (Collewijn & Tamminga, 1984; Rottach et al., 1996) and points to separate mechanisms of control for horizontal and vertical tracking. Because little noise is introduced in the final motor pathways (Lisberger, 2010), the difference between horizontal and vertical accuracies cannot be wholly explained by a difference in the brainstem motor nuclei. The eye muscle geometry, however, may place a larger computational load for vertical control to conform to Listing's law during motor planning (Angelaki & Dickman, 2003; Boeder, 1962; Simpson & Graf, 1981); therefore, it is possible that this larger computational load at the premotor stage contributes to decreased accuracy. The difference between horizontal and vertical tracking may also be generated at the level of visual processing, since there is a large contribution of sensory errors to the noise in the visuomotor response (Osborne, Lisberger, & Bialek, 2005).

Although there were differences in horizontal and vertical tracking, performance levels in the horizontal and vertical directions were parallel within individuals. Similar results have been demonstrated in clinical populations, including people diagnosed with schizophrenia and with bipolar disorder (Lipton et al., 1980). Research on infants also shows interdependence between the development of horizontal and vertical visual tracking mechanisms (Grönqvist, Gredebäck, & Hofsten, 2006). Taken together, these findings suggest a hierarchy of visuomotor processing and the existence of a high-level mechanism of control for horizontal and vertical visual tracking whereby computations are carried out in the two-dimensional visual space. This argument is consistent with the notion that visual tracking requires complex cognitive processes that are mediated by the cerebral cortex (Barnes, 2008; Chen et al., 2002; Kowler, 2011; Krauzlis, 2005; Lipton et al., 1980).

Accuracy of temporal prediction: Predictive timing

Evidence for the functional linking of vertical and horizontal tracking lends validity to our use of visual-tracking parameters based on polar coordinates. These parameters are uniquely associated with circular tracking, as opposed to linear or more complex two-dimensional tracking. With a precise method of eye position recording, large variability in the instantaneous radius of gaze trajectory (radial error variability) must indicate instability in the subject's spatial control, while large variability in the instantaneous angular phase (tangential error variability) must indicate a compound effect of instabilities in spatial and temporal control. Mean phase error, on the other hand, is an indicator of overall temporal accuracy. In a highly predictable circular tracking task, tangential error variability and mean phase error point to the individual's ability to sustain the state of synchronization between the external stimulus and the internally generated predictive drive.

We found that increases in phase lead, not lag, were associated with decreases in tracking accuracy assessed by gaze error variability, gain, and RMS errors. During tracking, the phase error was modulated with a sawtooth pattern, interposed by forward saccades. Poor tracking was characterized not by the mere presence of forward saccades but by the large and variable amplitudes of these saccades. Large forward saccades were anticipatory rather than corrective, landing as much as >10° of visual angle ahead of the target in some subjects. While catch-up saccades—that is, corrective forward saccades—compensate for phase lag, anticipatory saccades produce phase lead (Van Gelder et al., 1995). Since forward saccades repeatedly occurred before the gaze lagged the target sufficiently to offset the lead, the presence of large anticipatory saccades was associated with a large mean phase lead.

In our healthy subject cohort, we found no evidence for consistent positional errors that could serve as a threshold for initiating forward saccades during circular tracking. The saccades could not have been generated in reaction to the target image falling out of the foveal range, because the degrees of phase lag were generally smaller than those corresponding to the known range of latency for reactive saccades (Barnes, 2008; Rashbass, 1961; Westheimer, 1954). Thus, forward saccades must be triggered by an internal mechanism. It is possible that instability is induced when a high smooth pursuit eye velocity is generated, which can be ameliorated by generating large forward saccades, leading to slower velocities and greater stability.

Another possible explanation lies in the mechanism of attention. Attention is or can readily be allocated ahead of a moving target during predictive visual tracking (Khan, Lefèvre, Heinen, & Blohm, 2010; Lovejoy, Fowler, & Krauzlis, 2009; van Donkelaar & Drew, 2002). Such attention allocation is usually covert in that the gaze is maintained on the target; that is, the urge to shift the gaze to the center of attention away from the target is suppressed. It is possible that anticipatory saccades are the results of a failure in the top-down suppression mechanism, analogous to errors in antisaccade paradigms wherein suppression of reflexive automatic prosaccades is required (Munoz & Everling, 2004). In congruence with this hypothesis, the role of the right prefrontal cortex has been implicated in predictive visual tracking (Lekwuwa & Barnes, 1996a; Maruta, Suh, et al., 2010), antisaccade performances (Ettinger et al. 2008; Hwang, Velanova, & Luna, 2010), and attentional control (Corbetta & Shulman, 2002). Thus, a visual-tracking performance marked by excessive anticipatory saccades would suggest a neurologic dysfunction distinct from those marked by an increase in phase lag (Bronstein & Kennard, 1985; Heide, Kurzidim, & Kömpf, 1996; Keating, 1991; Lekwuwa & Barnes, 1996a, 1996b). Visual tracking of patients with chronic concussive syndrome (PCS) typically includes anticipatory saccades and phase lead (Maruta, Suh, et al., 2010) and, consistent with the hallmark symptom of PCS, attention impairments.

Measurement reliability

In the present study, changes in visual-tracking parameter measurements were observed between tests in individual subjects. Both errors associated with the measurement equipment and the inherent variability in motor behavior contribute to changes in measurements; therefore, the interpretation of these measurements needs to take measurement reliability into consideration. It has been argued that Pearson's product–moment correlation coefficient r is an inappropriate measure of reliability because r is an index for association, not agreement, between two variables (Bartko, 1991; Bland & Altman, 1986). ICC, a commonly used index of relative reliability, also fails to describe the precision with which a measurement can be clinically interpreted—that is, absolute reliability. We addressed absolute reliability with the use of the 95 % confidence interval of repeatability associated with each of the visual-tracking parameters.

The smaller the 95 % confidence interval of repeatability, the more precise the measurement is. However, the precision required to distinguish a measurement as different from other measurements depends on the value of the measurement in relation to the shape of the parameter distribution. Because of the skew characteristics of the visual-tracking parameter distributions, the relative precision was low for the range applicable to most subjects but high for values associated with a few extremely poor performers. Consequently, instances of extremely poor performances were salient and were identifiable outside the margin of error within the normal subject group. Given that our primary goal of using visual-tracking assessment is to delineate the normal population and, as a result, identify exceptions, the method and indices described in this study have potential utility in quantifying and monitoring attention function involved in dynamic visuomotor synchronization. This approach will gain further strength as normative standards become better defined with consideration of factors such as age and gender.

Conclusion

We quantified the performance of maintenance-period predictive circular visual tracking using several measures. Successful visual tracking requires dynamic cognitive synchronization of the internally generated prediction with the external stimulus, yet we found varying degrees of visuomotor synchronization among normal subjects. Disruptions of gaze–target synchronization were associated with anticipatory saccades that

suggested impaired predictive timing. Within the ranges of variations in the synchronization indices, there was a clear difference between good and poor performers. The interindividual performance variability likely reflects varying levels of attentional control among individuals. Thus, quantification of dynamic visuomotor synchronization in an individual may provide a sensitive and reliable attention metric. The quantification of circular visual-tracking performance provided here establishes the essential testing parameters for assessing normal and impaired attention.

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